
Usefulness of Acetylsalicylic Acid in Diabetic Vascular Complications

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Low dose acetylsalicylic acid (aspirin) has been shown to reduce the risk of MI and thrombotic stroke in patient at high risk of vascular death. The deaths from heart disease and stroke are more frequent in diabetics than in non-diabetics. Does aspirin work in diabetic patients as a primary prevention strategy? This article summarizes literature and the role of aspirin therapy in diabetic patients.

Diabetic patients have two to four folds increase in the risk of dying from the complications of cardiovascular diseases¹. Both men and women are at increased risk. Atherosclerosis and vascular thrombosis are the major contributors and it is accepted that platelets are contributory. Among the patients with type 2 diabetes, microalbuminuria or proteinuria further doubles the cardiovascular risk². In type 2 diabetes, the increased risk is present before fasting hyperglycemia is seen. These individuals often have a sedentary life style, poor physical conditioning, insulin resistance, obesity, hypertension, and dyslipidemia, and are in a prothrombotic state³. Chronic hyperglycemia is then added to these risk markers. An all-inclusive approach that focuses on early risk factor (or marker) identification and management to prevent or delay accelerated atherosclerosis and thrombosis in diabetes is an attractive strategy.

Blood coagulability and atherogenesis:

There is increasing evidence that diabetes predisposes to procoagulant (thrombogenic) changes in the blood and that these may favour increased blood viscosity and atherogenesis in diabetic and non-diabetic populations⁴. Diabetes is associated with several defects of coagulation and fibrinolysis, which overall predisposes to a procoagulant, thrombogenic tendency⁵. Some studies have suggested that fibrinogen levels are increased in various populations at in-

creased risk of coronary heart disease, including diabetic subjects⁶. Raised fibrinogen concentrations are thought to favour coagulation, and also to increase blood viscosity (of which fibrinogen is a major determinant) and to encourage platelet activation and adherence to the endothelium⁵.

Secondly, in addition to the accelerated atherosclerosis there is increased tendency of thrombosis in diabetic patients. Platelet aggregation, fibrinogen, von Willebrand factor, factor V, VII, X are found to be increased⁷. There have also been reports that fibrinolytic activity is decreased in the diabetic patients⁸. Increased blood viscosity can lead to increased incidence of the thrombosis.

It is reported that platelets from people with diabetes are often hypersensitive *in vitro* to platelet aggregating agents⁹. A major mechanism appears to be operating through increased production of thromboxane, a potent vasoconstrictor and platelet aggregator substance produced by platelets. Investigators have found evidence *in vivo* of excess thromboxane release in type 2 diabetic patients with cardiovascular disease. Aspirin blocks thromboxane synthesis by acetylating platelet cyclo-oxygenase and has been used as a primary and secondary strategy to prevent cardiovascular events in nondiabetic and diabetic individuals¹⁰.

Pharmacology of aspirin's action on platelets:

It has long been recognized that aspirin induces a long-standing platelet defect that is characterized by a prolonged

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bleeding time. The major mechanism is aspirin's permanent inactivation of prostaglandin G/H synthetase, the enzyme that catalyses the conversion of arachidonic acid to prostaglandins G2 and H2. These are the precursors of thromboxane.

Aspirin leads to an immediate inhibition of thromboxane synthesis in the platelets of normal subjects and diabetic individuals. The effect is rapid and probably begins in the hepatic portal system as soon as aspirin is absorbed from the gastrointestinal tract. Because platelets do not have the synthetic machinery to make new protein, there is no enzyme recovery in exposed platelets during their life span, which averages 8-10 d. Each day, new platelets enter the bloodstream at a rate of ~10% per day. This rate may be accentuated in people with diabetes, leading to a special consideration about aspirin therapy in these patients¹¹. Several studies have suggested that drugs acting on platelet function can reduce albumin excretion in patients with proteinuria.

EFFICACY

Primary prevention trial:

The U.S. Physicians' Health Study conducted by Patrono *et al.*¹² had shown that aspirin therapy is as effective in diabetic men as in non-diabetic men. This was a randomised double-blind placebo-controlled trial in adult men to determine whether low-dose aspirin (325 mg on alternative days) would decrease cardiovascular mortality. Results from 22,071 participants, with an average follow-up time of ~5 y, have been reported. There was a 44% reduction observed in the risk of myocardial infarction in the entire group.

Subgroup analyses were done in a group of 533 diabetic individuals randomised to aspirin or to placebo. Myocardial infarction occurred in 11/275 (4%) of diabetic men assigned to aspirin therapy and in 26/258 (10.1%) diabetic men assigned to placebo therapy. In nondiabetic men, 231/10,763 (2%) had myocardial infarction on placebo therapy, while 128/10,750 (1.2%) had this event on aspirin therapy. Although the diabetic men were at substantially higher risk for infarction than the nondiabetic men, the relative risk of myocardial infarction for diabetic individuals on aspirin therapy was 0.39 while it was 0.60 in the entire cohort. The difference between these risk reductions was not significant ($P=0.22$), indicating that aspirin therapy was as effective in diabetic men as in nondiabetic men.

Primary and secondary prevention trial (retinopathy

study):

Also known as "Early Treatment Diabetic Retinopathy Study (ETDRS)", this study concluded that aspirin at a dose of 650 mg/day had neither slowed the progression of retinopathy nor the risk of bleeding from new vessels. Secondary prevention trial had shown that prolonged aspirin therapy offer significant protection against MI, stroke and vascular diseases. The study had also shown that in diabetic patients there is reduction in the non fatal MI and in stroke were about 1/3rd and the risk reduction was about 1/6th in vascular deaths.

Dosage:

It has been shown that a dose as low as 75 mg of enteric coated aspirin is just as effective as higher doses of either plain or enteric coated aspirin in inhibiting thromboxane synthesis². When the platelet turnover is rapid, as is reported to occur in diabetes mellitus, the steady plasma concentration from enteric coated preparation allows constant suppression of thromboxane synthesis. Moreover the cyclo-oxygenase enzyme system is exquisitely sensitive to aspirin doses as low as 75 mg daily and has been demonstrated that endothelial prostaglandin release is not inhibited at these low doses¹³. There are some suggestions that, because of increased turnover of the platelets, diabetic patients need higher doses of aspirin and that 300 mg of enteric coated aspirin daily may be a better regimen than 75-100 mg daily used in non diabetic patients.

Safety:

A major risk of aspirin therapy is GI mucosal injury and GI hemorrhage. These effects are dose-related and are reduced when the enteric preparations of 75-325 mg are used once daily. Antiplatelet trialists collaborative study showed that aspirin therapy was not associated with an increased risk for retinal or vitreous hemorrhage¹⁴. A low dose of aspirin is a very weak inhibitor of renal prostaglandin synthesis and has no clinically significant effect on renal function or on blood pressure control.

Recommendations:

It is recommended to use aspirin as a secondary prevention strategy in diabetic men and women who have evidence of large vessel disease. This includes diabetic men and women with a history of MI, vascular bypass procedure, stroke or transient ischaemic attack, peripheral vascular disease, and/or angina. In addition to treating the primary cardiovascular risk factors identified, consider aspirin therapy as primary prevention strategy in high-risk men and women with

type 1 or type 2 diabetes mellitus. This includes diabetes mellitus subjects with;

1. A family history of coronary heart disease, cigarette smoking, hypertension, obesity, albuminuria (micro or macro) and lipids (cholesterol >200 mg/dl, LDL >130 mg/dl, HDL <40 mg/dl and TG >250 mg/dl).
2. Use enteric coated aspirin tablets in doses of 75–325 mg/day.
3. The following may not be candidates for aspirin therapy:
 - a. Diabetic individuals under the age of 30 y with out cardiovascular risk factors.
 - b. People with aspirin allergy, bleeding tendencies, patients on anticoagulant therapy, recent GI bleeding and clinically active hepatic disease.

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